News And Comment

An International Conference on Recombinant DNA was held at Wye Agricultural College, United Kingdom, from April 1 to 4. The purpose of this meeting, sponsored by the Royal Society and COGENE (see Bulletin, Vol. 2, No. 1), was to review the current status of recombinant DNA research and technology. The proceedings of this meeting are to be published later this year by Pergamon Press. The following is the talk presented by the Director of NIH.

A History of the Recombinant DNA Guidelines in the United States

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Introduction

On December 16, 1978, a telegram purporting to be from the Vatican was hand-delivered to the office of Joseph A. Califano, Jr., Secretary of Health, Education, and Welfare. "*Habemus regimen recombinatum,*" it proclaimed, in celebration of the end of a long struggle to revise the NIH Guidelines for Research Involving Recombinant DNA Molecules. It was not the first telegram the Secretary had received on this subject. From Peking the preceding June, I had responded to his cabled instructions concerning proposed revisions of the Guidelines which I had taken to China. The U.S. liaison officers found my reply inappropriate for transmission, but I delivered it on my return, imprinted on a rice paper temple-rubbing.

These sophomoric tricks were moments of comic relief in a three-year period of coping with the scientific, political, and legal problems created by the advent of the "new biology." The following pages summarize my impressions of this turbulent experience.

My personal history of the DNA Guidelines in the United States recognizes three phases to date. Phase I is the period between the early concern about possible hazards of recombinant DNA technolgy and the delivery to NIH of proposed rules for conducting research. Phase II covers the promulgation of the NIH Guidelines in 1976 and the thirty months before their official revision. Phase III began on January 2, 1979, with a new set of rules painfully formulated during this unprecedented curtailment of experimentation in biology.

The End of the Beginning

In this collection are reminiscences of the first apprehensions (1973), the decision to develop guidelines (1974), the Asilomar agreements (1975), and the exhausting constructions of the NIH Recombinant DNA Advisory Committee (RAC). Three versions of guidelines had emerged from RAC meetings after Asilomar. In La Jolla, Calif., on December 5, 1975, the committee, with the "variorum edition" before it, finally succeeded in scaling conjectural hazards by parliamentary procedure. The Chairman Hans Stetten went to the telephone to inform the NIH Director in Bethesda that the nation had aquired rules for recombinant DNA research. Much later I was told how he had returned to the conferees, shoulders drooping, success drained from his face. "He wants to have a public hearing on them," he mumbled.

Public Airing Begins

From the beginning the decision to "go public" was variously understood and was resented by many. After all, the Director, NIH, has long had authority to promulgate guidelines for investigators the agency supports. There is no requirement for hearings or public comment. I became aware of new responsibilities headed my way sometime in the autumn of 1975, when I had been Director for only two or three months. At that time, I had barely heard of restriction enzymes and couldn't even have explained the crucial distintions between Federal *guidelines* and *regulations*. From the first I was inclined—and after a little study and consultation, quite determined—to air in an open and public manner the scientific and social issues. This was the only way to decompress rising tensions and to prepare to defend whatever actions would be taken against certain criticism.

The Director's Advisory Committee (DAC) was convened in February 1976 for public discussion of the Guidelines. The transcript, like all the other relevant documents on the subject, is available in the "public record" published by NIH. The hearing demonstrated the difficulties of holding a town meeting on molecular biology and exposed the full range of opinions on the risks of the new technology. It was apparent that our decisions would have to run a gamut of adversarial reactions and, in the end, might well be tested in the courts. After the hearing, the voice of Judge Bazelon lingered longest in my mind: "...the healthiest thing that can happen is to let it all hang out, warts and all, because if the public doesn't accept it, it just isn't worth a good damn."

We made some changes in the proposed Guidelines after the DAC meeting, mainly adding administrative structure. We then set out to acquaint key people and agencies with the details, for NIH supported most but by no means all of the affected research. The widening circle included the National Science Foundation, the Department of Agriculture, other Federal agencies whose authorities were crossed by the NIH Guidelines, the staffs of Congressional committees with jurisdiction over biomedical research, and representatives of industry doing what private research of this sort there was at the time.

Issuance of the Guidelines

The NIH Guidelines were issued on June 23, 1976. It was front page news, but the reactions were muted. We also established the Office of Recombinant DNA Activities (ORDA), under the direction of William Gartland.

The NIH Guidelines were just that —guidelines, not regulations, which have more of the force of law. The verbs tended to be "shoulds," though some "shalls" had been substituted after the February hearing. It was stated that the Guidelines would be frequently revised, but no special procedures for doing so were laid out. They were expected to evolve as understandings of the subject grew. As it turned out, it was not the subject of the Guidelines, but "due process" for changing and administering them, which became the focus for opposition to the research. For the next two and a half years, the Guidelines were to be practically frozen, while the science expanded impatiently within.

Extension of the Guidelines Beyond NIH

NIH had no illusions that it was creating guidelines for all the recombinant research in the world. Scientists are citizens of different nations whose laws can supersede intellectual accord. Even within the United States, extension of the same rules to all laboratories could not be achieved by any simple move.

Two different kinds of protest about this imcompleteness were brewing in 1976-78. One encouraged extension of the jurisdiction of state and local communities to regulation of laboratory research, a legal area hitherto unexploited. The other sought to persuade DHEW, its Food and Drug Administration (FDA), and other regulatory agencies to use certain narrow authorities to force compliance with common rules. If that failed, the Department was to seek a Federal law to that end. Some fervent advocates of legislation fought for preempting local jurisdictions from enacting more stringent standards if they wished. Others just as vehemently opposed Federal preemption. A Balkanization of recombinant DNA research was one of the most serious and extraordinary threats of this period.

In May 1976 we informed our Department superiors about our intention to issue guidelines, and urged then-Secretary David Mathews to ask the President to direct all relevant Federal agencies to coordinate recombinant DNA activities through an interagency committee. Mathews agreed, but no words emanated from the White House. In July, Senators Kennedy and Javits addressed a letter to President Ford advocating the extension of NIH Guidelines to all Federal and private research. Local hearings in Cambridge, Mass.; Ann Arbor, Mich.; San Diego, Calif.; and New York added to a sense of urgency.

The President's letters were finally dispatched in September, and the Federal Interagency Committee on Recombinant DNA Research was promptly convened in Bethesda. The research agencies readily agreed to use the NIH Guidelines for the research they suppored or conducted. The committee then undertook to examine the regulatory authorities of each of the member agencies

and to develop recommendations for possible new legislation. Later the committee would examine patent policy and the international aspects of regulating DNA research.

NEPA and the Friends of the Earth

A full discussion of the National Environmental Policy Act (NEPA) with reference to laboratory research in general and to how the NIH Guidelines for recombinant DNA research became involved would fill a volume. NEPA, a law passed in 1969, requires the Federal agencies to determine whether contemplated actions will significantly affect the environment. If so, the action must be heralded by an Environmental Impact Statement (EIS). In the spring of 1976 we were made aware that if we released the Guidelines before issuing an EIS, we could be charged with violating NEPA.

Although an EIS had become common in proposals to level mountains or build dams, the adaptation of NEPA to conjectural hazards of laboratory research was a nightmare. The situation was aggravated by ambiguous and arbitary procedures for implementing NEPA within DHEW. The tortoise-like march from *draft* to *final* EIS could take years.

But delaying the issuance of the Guidelines pending completion of the EIS process was never an alternative. The voluntary agreements made at Asilomar were losing their hold on the scientists, confusion was mounting, and dissidents in various communities threatened to obtain either local regulation or prohibition of the research if Federal standards were not quickly forthcoming. It was obvious that the public interest would be better served—and the opportunity of scientists to continue experiments, better protected— with guidelines than without them, even if an EIS were not published until after their issuance.

We therefore released the Guidelines in June with an announcement that an EIS was to follow. The draft EIS was filed in September 1976, the final one in October 1977. On May 1977 two suits against NIH were launched in separate Federal courts. One, brought by an organization called The Friends of the Earth, sought to enjoin all recombinant research. The other sought to block the Rowe-Martin risk assessment study. The final EIS was entered as part of the Government's defense in the latter suit (Mack v. Califano). In finding for the Government in March 1978, the Court concluded that NIH, in its EIS, had indeed "taken a hard look" at the consequences of experiments with recombinant DNA. The plaintiff was denied an injuction.

Thrust Toward Legislation

A bill was introduced in the Senate (S. 621) in February 1977 by Senator Bumpers (D., Ark.), with a companion bill in the House by Rep. Ottinger (D., N.Y.). They were the first of 12 bills to regulate DNA research submitted to the 95th Congress. On February 23, representative scientific leaders were invited to NIH to read selected passages of the proposed new legislation, including heavy penalty provisions. Two weeks later the last traces of their indifference would be dispelled by the acrimonious tone of a forum on "genetic engineering" at the National Academy of Sciences.

The following May the Interagency Committee conveyed to the new HEW Secretary, Joseph A. Califano, Jr., its conclusions that a Federal statute would be required if the Guidelines were to be extended to all recombinant research in the country. It was also offered the elements of what it considered an "ideal" law—elements that were quickly converted to an Administration bill introduced by Senator Kennedy (S. 1217) on April 1, 1977. Kennedy then revised the bill radically. In an intensive reaction to this and other proposed laws, scientists and their organizations soon made strong appeals to the Congress. The ardor of the legislators for statutory regulation cooled progressively during 1977-78.

Revision Is Needed

Within six months of their appearance, the NIH Guidelines clearly needed revision. The molecular biologists who had constructed them, if given that chance again, would surely have engaged other disciplines on the route from Asilomar to Bethesda. Especially lacking had been the counsel of experts on infections, who had a better perspective of the improbability that *E. coli* K-12 could be converted into an epidemic pathogen. And more thought should have been given to the containment levels for dealing with viral DNA, to the prohibitions, and to the coverage of organisms known to exchange DNA in nature.

It is also notable that the guidelines constructed at about the same time in the U.S. and the U.K. were quite different in form. The Americans wrote an extensive codification and the British opted for common-law evolution of minimum rules. Both sets, however, were meant to be interpreted and administered centrally, by a GMAG or an ORDA. The U.S. scientists did not want local committees to second-guess their experimental protocols. More comfortable with central decision-making by study sections in Bethesda, they preferred ORDA's interpretations and administration.

But delays in administrative actions were inevitable. The requirement for prior NIH approval of all changes in ongoing projects particularly irked investigators. In rejecting at the start nearly all suggestion of control by their institutions, the scientists had made it difficult to regain a proper balance between local application and national

standards.

As a broker between the molecular biologists and the various public interests, NIH also failed to perfect the Guidelines before issuing them. We did not incorporate mechanisms for revision. Discretionary powers to make interpretative judgments and minor changes, essential in so complex and fast-moving a subject, were lacking. There were reasons, however, for avoiding imitation of the formal and formidable procedures of the regulatory agencies. The more we embedded the Guidelines in inflexible administrative molds, the less chance there would be for timely accommodation to the tide of new information that was already rising.

Revision Begins

In January 1977 the RAC commenced to prepare a revised set of Guidelines. A workshop was held in June at Falmouth, Mass., to synthesize old and new information about bacterial host-vector systems. In September the proposed revision—a complete rewriting of the text—was formally presented to me and published in the *Federal Register*. A two-day hearing was held in December 1977 at which the RAC members defended their proposed changes. Most critics raised questions of process; but some containment levels were severly challenged, and additional meetings of experts on viruses and plant pathogens led to further alterations.

In Departmental clearance, the revised Guidelines encountered more difficulties than the original. Recombinant DNA research had emerged as a scientific issue with immense appeal to laymen, and Secretary Califano's staff took a strong and sophisticated interest in how all relevant law and administrative practices pertained to the new draft. By now, some dissidents and a militant fraction of the environmental movement had also launched a concerted campaign to exact, if science wished to proceed, a more generous tax in procedure.

On July 28, 1978, the proposed revision, accompanied by our environmental impact assessment and a Director's decision paper, was publised in the *Federal Register*.An introductory memorandum from the Secretary invited the public to comment and announced that, after a 60-day period, there would be another hearing chaired by Peter Libassi, the HEW General Counsel.

Revision Completed

The Libassi hearing took place on September 15 at the HEW headquarters in Washington. NIH staff and I—the "Kitchen RAC"—then dissected the comments received in testimony and 170 letters, and joined in numerous discussions with Mr. Libassi and his committee. Special meetings were also held with a group of environmentalists who wished to reinforce some of their earlier demands. We also met with representatives of pharmaceutical firms, other Federal research agencies, and members of institutional biosafety committees to discuss their problems with the proposed revisions. A culmination of the Libassi hearings was the reconstitution of the RAC to broaden its public (nonscientific)j membership and to combine the technical and policy reviews, usually carried out at NIH in a two-tiered process. The appointment of RAC members was shifted from the NIH Director to the HEW Secretary. The revised Guidelines were released late in December, to become effective on January 2, 1979.

The detailed analysis led by the HEW General Counsel had added a few weeks to the long period of revision. One result was a modest additional burden of procedural safeguards, but this was offset by the removal of any grounds for complaint from the most fervent dissident that the public had not been exhaustively consulted.

There were important achievements in the revision. The new Guidelines contain provisions for continuous and orderly evolution of the rules—even to their eventual elimination when the need passes. Many experiments now judged to be harmless are exempt, and containment for other kinds of experiments has been reduced. Also, the discretion and responsibility for observing the rules are beginning to return to the research institutions, where I believe they belong.

Attempts to enact statutory regulation of recombinant DNA experimentation in the United States need not be revived soon. One hopes they won't, for some of the medieval features of the first bills tended to reappear as later ones passed through the committees. A problem remains, however, in the limits on NIH's ability to protect proprietary data submitted to the RAC. Actions taken by Secretary Califano upon release of the Guidelines, to have regulatory agencies (the Food and Drug Administration, the Environmental Protection Agency, etc.) use their existing authorities to extend the Guidelines over research in the private sector, have been helpful in exploring an alternative to a new law.

Moral

It is possible that the "recombinant DNA affair" will someday be regared as a social aberration, with the Guidelines preserved under glass. Even so, we can say the beginnings were honorable. Faced with real questions of theoretical risks, the scientists paused and then decided to proceed under caution. That decision gave rise to dangerous overreaction and exploitation, which gravely obstructed the subsequent course. Uncertainty of risk, however, is a compelling reason for caution. It will occur again in some areas of scientific research, and the initial response must be the same. After that, the lessons learned here should help us through the turbulence that is sure to come.